REMARKS/ARGUMENTS

I. Status of the Claims

Claims 1-5, 10-11 and 21-22 are currently pending in this application. Upon entry of this amendment, claims 1, 2 and 10 are amended, and new claims 23-31 are added. Claims 1-5, 10-11 and 21-31 are thus pending following entry of this amendment.

Amended claims 1, 2 and 10, and new claims 23-31 are supported throughout the specification, including, for example, the following paragraphs:

Claim 1: paragraphs 143 and 114;

Claim 10 paragraph 152;

Claims 23-25: paragraph 143;

Claims 26-28: paragraph 143; and

Claims 29-31: paragraph 158.

Claim 2 has been amended for clarity by replacing "nucleotide residues" with "nucleotides". Claim 10 has been amended to change the claim dependency. No new matter is added by these amendments.

II. Claim Rejection under 35 U.S.C § 102

Claims 1 and 10-11 were rejected under 35 U.S.C § 102(b) as allegedly anticipated by Bonaldo et al. (Genome Res 6:791-806, 1996). Applicants respectfully traverse this rejection.

The Office indicated that Bonaldo et al. described the 558 nucleotide sequence at the 3' end of SEQ ID NO:1 (i.e., GenBank entry BM690735). This assertion is not correct: The

Bonaldo reference did not describe or refer to the reference sequence. Rather, BM690735 has a publication date of February 28, 2002 and is not prior art to the present application. The BM690735 GenBank entry includes a citation of the Bonaldo et al. reference and it is possible this gave rise to confusion. However, the Bonaldo et al. reference was cited in the GenBank entry only to describe how the cDNA library containing this nucleic acid segment was constructed.[1]

For the convenience of the examiner, a copy of the GenBank entry showing the publication date, as well as email from the NCBI confirming the date are attached.

GenBank entry BM690735 was published well after the filing date of the instant application and is not prior art. The Bonaldo et al. reference did not describe or suggest the claimed polynucleotide. Accordingly, there can be no anticipation. Applicants respectfully request that the Examiner withdraw the rejection of claims 1 and 10-11 under 35 U.S.C § 102(b).

III. Claim Rejections for Alleged Lack of Utility

The sole remaining issue is the assertion by the Office that the claimed invention lacks utility. Applicants respectfully request that the Examiner reconsider this rejection in view of the comments below. A claimed invention is patentable under 35 U.S.C. § 101 when the invention has specific, substantial and credible utility.

A. The Utilities of the Claimed Invention

The claimed polynucleotides encode an extracellular interphotorecetor matrix (IPM) proteoglycan, IPM150, which is expressed in human neural retina. The specification provides evidence that IPM proteoglycans, like IPM150, play a role as an adhesive element bridging the retinal pigment epithelium (RPE)-retina interface, and that changes in IPM

[1] The GenBank entry also indicates that the inventor of the present application, Dr. Hageman, was the source of the tissue used to make the library from which the BM690735 sequence was obtained.

proteoglycans are associated with ocular diseases and disorders and diseases, such as retinal detachment, chorioretinal degeneration, and macular degeneration. Therefore, the claimed polynucleotides are useful for detecting alterations or abnormalities in level of expression, composition and/or sequence of IPM150 polynucleotides and polypeptides in various ocular diseases and disorders. As such, the claimed polynucleotides can be:

(1) included in nucleic acid arrays with nucleic acids from other genes having roles in ocular diseases or disorders:

(i) to analyze disease-related gene expression in ocular tissues or cells; or

(ii) to analyze candidate drugs for roles in modulating ocular diseases and disorders (i.e., drug screening);

(2) used to generate anti-IPM150 antibodies, which are useful for:

(ii) isolating IPM150 polypeptides (e.g., by immunoaffinity chromatography);

(ii) detecting IPM150 polypeptides in ocular tissues or cells (e.g., by Western blot hybridization, immunohistochemistry, or immunostaining); or

(iii) immunostaining specific regions of human neural retinal tissues;

(3) used to produce IPM150 polypeptides, which are useful for drug screening for ocular diseases and disorders; and

(4) used to re-establish retinal adhesion and/or promote photoreceptor survival (e.g., in the case of retinal detachment).

This list is not comprehensive or limiting and only provides examples of the many utilities of the invention.

B. The Utilities of the Claimed Invention Are Specific

A specific utility is one that is specific to the subject matter claimed, not one that would be applicable to the broad class of the invention. According to the MPEP at 2107.01, a claim to a polynucleotide whose use is disclosed simply as a "gene probe" or "chromosome marker" is not considered to be specific in the absence a disclosure of a specific DNA target. The claimed polynucleotides are not disclosed as a "gene probe" or "chromosome marker" without a specific DNA target, but are disclosed as being useful for detecting alterations or abnormalities in level of expression, composition and/or sequence of a specific target, the interphotoreceptor matrix proteoglycan IPM150, in a specific tissue setting.

The foregoing asserted utilities are clearly not simply general utilities, but instead are specific to a particular class of nucleic acids, namely, those that encode genes that are expressed in the retina and play a role in retinal adhesion. Although not required, multiple specific utilities are asserted. Thus, the specification satisfies the requirement that it include an assertion of a specific utility.

C. The Utilities of the Claimed Invention Are Substantial

A substantial utility is one that has a "real world" use. A utility that requires or constitutes carrying out further research to identify or reasonably confirm a "real world" context of use is not considered substantial. The asserted utilities do not require or constitute carrying out further research, but have direct "real world" utilities in that the claimed polynucleotides can be used in nucleic acid arrays, to generate antibodies, and to produce polypeptides for uses described above, as well as to detect alterations or abnormalities in level of expression, composition and/or sequence of IPM150 in ocular diseases and disorders. One skilled in the art would recognize that detecting such alterations or abnormalities constitutes a significant "real world" use because the specification provides a clear association between the claimed polynucleotides, retinal adhesion, and certain ocular diseases and disorders. Thus, the specification satisfies the requirement that it include an assertion of a substantial utility.

D. The Utilities of the Claimed Invention Are Credible

The remaining issue is whether the specific and substantial utilities asserted for the claimed polynucleotides are credible, that is, whether one skilled in the art would find the asserted utility believable based on the totality of the provided evidence and reasoning. As stated in the MPEP at 2107.02, "an assertion is credible unless (A) the logic underlying the assertion is seriously flawed, or (B) the facts upon which the assertion is based are inconsistent with the logic underlying the assertion."

It is clear to one skilled in the art that the claimed polynucleotides, IPM150 polynucleotides, encode extracellular IPM proteoglycans[2] that are expressed in the human neural retina.[3] It is also clear to one skilled in the art that extracellular IPM proteoglycans, like IPM150, play a role as an adhesive element bridging the RPE-retina interface.[4] Because changes

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[2] The claimed IPM150 polynucleotides have distinctive features indicative of extracellular proteoglycans, including:

(1) consensus sequences for N- and O-linked glycosylation (see, e.g., paragraph 78), which indicate that the encoded proteins are proteoglycans;

(2) consensus sequences for hyaluronan binding domains (see, e.g., paragraph 80), which indicates that the encoded proteins are proteoglycans;

(3) lack of hydrophobic regions, which indicate that the encoded proteins are secreted into the interphotoreceptor space (see, e.g., paragraph 81); and

(4) presence of EGF-domains, which are present in many extracellular matrix proteins, that are associated with cell survival (see, e.g., paragraph 79).

[3] Applicants have provided direct evidence that the claimed polynucleotides, and the proteins encoded by them, are specifically expressed in the human neural retina. Example 1 shows that:

(1) IPM150 polynucleotides are expressed in human neural retina; and

(2) IPM150 polypeptides are present in the IPMC protein preparations from human neural retina.

[4] The specification provides evidence and reasoning indicating that extracellular IPM proteoglycans play a role as an adhesive element bridging the RPE-retina interface, including:

(1) the relationship between the retina and choriod is crucial to proper eye function, and ocular diseases or disorders, such as retinal detachment, chorioretinal degeneration, and macular degeneration result when this relationship is compromised (see, e.g., paragraph 14);

(2) molecules in the IPM located between the retina and choroid are likely important in maintaining the above relationship (see, e.g., paragraph 16);

in IPM proteoglycan composition correlate with proper retinal adhesion and the etiology of photoreceptor demise and are associated with drusen[5], it is clear to one skilled in the art that the claimed polynucleotides are associated with ocular diseases or disorders, such as retinal detachment, chorioretinal degeneration, and macular degeneration. Based on the above, one skilled in the art would find it credible that the claimed polynucleotides can be useful in nucleic acid arrays, to generate antibodies, and to produce polypeptides to detect alterations or abnormalities in level of expression, composition and/or sequence of IPM150 in ocular diseases and disorders.

Applicants draw the Examiner's attention to two articles that lend support to the asserted utilities. In van Lith-Verhoeven et al. (Invest Ophthalmol Vis Sci 45:30-35, 2004), the authors state, referring to IPM150[6], that chondroitin-6-sulfate rich glycosaminoglycans around cone photoreceptor cells "appear to play a crucial role in the physical attachment of the neural retina to the RPE." In a review article by Schwartz and Domowicz (Glycobiology 12:57R-68R, 2002), it is reported that certain human skeletal defects are associated with mutations in proteogylcan genes. Because such genetic defects in proteoglycan genes were known at the time of filing this application, Applicants respectfully submit that one skilled in the art would have

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(3) IPM molecules play a critical role in maintenance of retinal photoreceptor cells, and IPM proteoglycans mediate photoreceptor cell adhesion (see, e.g., paragraph 16); and

(4) specific components of the IPM act as major adhesive elements bridging the retinal pigment epithelium (RPE)-retina interface (see, e.g., paragraph 18).

[5] The specification provides evidence and reasoning indicating that changes in IPM proteoglycan composition are associated with ocular diseases and disorders, including:

(1) there is a close correlation between integrity of proteoglycans associated with IPM cone matrix sheaths and proper retinal adhesion (see, e.g., paragraph 18);

(2) changes in the IPM composition correlate with the etiology of photoreceptor demise in certain ocular degenerations (see, e.g., paragraph 21); and

(3) changes in IPM proteoglycan composition are associated with drusen, extracellular deposits found in association with macular degeneration (see, e.g., paragraph 22).

[6] The IPM150 gene is also known as *IPMG1* and SPACR (see references cited in van Lith-Verhoeven et al.)

recognized that the claimed polynucleotides, more likely than not, have the asserted utilities. For the convenience of the Examiner, copies of these articles are enclosed.

The Examiner contends that the Applicant's asserted utilities are conjecture because IPM150 is expressed in tissues other than the retina, allegedly no pathological processes associated with IPM150 are provided, and Applicants' own published work is said to support a finding that the nucleic acid encoding IPM150 is used only as the subject of further research. Applicants respectfully submit that the Examiner has used inappropriate tests or reasoning to analyze the credibility requirement, and address these contentions in turn.

First, the possibility that IPM150 is expressed in other tissues has no relevance to the role that IPM150 plays in the retina. Example 1 discloses that IPM150 polynucleotides and polypeptides are specifically expressed in human neural retina. Example 1 also discloses that dot blot analyses indicate that "IPM150 mRNA, *or transcripts with a similar nucleotide sequence* are present in adult lung, liver, thymus and small intestine" (emphasis added, see paragraph 346). The mere fact that an IPM150 probe hybridizes to RNA in tissues other than the retina does not alter the conclusion one skilled in the art would make based on the evidence and reasoning provided in the specification.. One skilled in the art would conclude IPM150 plays a role in retinal adhesion, as taught by the instant specification.

Second, the specification does provide pathological processes that are associated with IPM150. The specification teaches that the claimed polynucleotides play a role in proper retinal adhesion, which is compromised in specified ocular diseases and disorders. As such, the claimed polynucleotides are useful for detecting alterations or abnormalities in level of expression, composition and/or sequence of IPM150 in ocular diseases and disorders. The claimed polynucleotides are useful for detecting IPM alterations or abnormalities independent of whether IPM150 is causative for, or associated with, the particular ocular disease or disorder.

The Examiner's attention is drawn to the attached van Lith-Verhoeven et al. article, which reports the linkage between the *IPMG1* gene, in particular a mutated form of the

encoded IPM150 polypeptide, and a human ocular disease. Thus, one study subsequent to the filing of the instant application has borne out Applicants' assertion that the currently claimed nucleic acids are useful to analyze ocular diseases and disorders, consistent with the teaching of the specification (see, e.g., paragraph 219).

Third, the statement in Kuehn et al. (Molecular Vision 6:148-0156, 2000), that cloning of murine IPM150 may be considered "a first step towards the development of experimental murine models, which may eventually be used to elucidate the mechanisms underlying retinal adhesion and photoreceptor survival," does not indicate that the asserted utilities for the claimed polynucleotides constitute further research. Applicants have asserted "real world" uses for the claimed IPM150 polynucleotides that are independent of their use in developing mouse models for mechanistic studies.

The Examiner has contended that including the claimed polynucleotides in nucleic acid arrays is not a substantial utility because no correlation is disclosed between an altered form or level of the claimed polynucleotides and any disease or disorder, so that "results of gene expression monitoring would be meaningless without significant further research." Applicants respectfully disagree. The Examiner has used an incorrect standard to analyze this asserted utility. There is no requirement that altered forms or levels of IPM150 polynucleotides must be associated with a particular ocular disease or disorder. Applicants have provided a reasonable correlation between the claimed polynucleotides and the asserted utilities, and it is sufficient that that nucleic acid arrays be useful in detecting alterations or abnormalities in level of expression, composition and/or sequence of IPM150 in ocular diseases and disorders.

For the reasons provided above, Applicants respectfully request that the rejection of the pending claims as allegedly lacking utility be withdrawn.

IV. Information Disclosure Statement

Applicants note that they did not receive initialed copies of the information disclosure statements mailed January 30, 2004 and February 2, 2004 showing that the documents

cited therein have been considered by the Examiner. Applicants request that if the Examiner has not already done so that the cited documents be considered and that checked off copies of these two information disclosure statements be provided with the next communication.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,

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Attachments
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